

NDA 20-597/S-018

AUG 25 2000

Pharmacia & Upjohn Company
Attention: Gregory G. Shawaryn
Regulatory Manager, Regulatory Affairs
7000 Portage Road
Kalamazoo, MI 49001

Dear Mr. Shawaryn:

Please refer to your supplemental new drug application dated July 25, 2000, received July 26, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xalatan® (latanoprost ophthalmic solution) 0.005% (50 mcg/mL).

This supplemental new drug application provides for the addition of “Complimentary package-not for sale” to the carton labels and “Sample” to the bottle labels of the physician samples.

We have completed the review of this supplemental application and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling of the bottle and cartons submitted July 25, 2000.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated “FPL for approved supplement NDA 20-597/S-018.” Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a “Dear Health Care Practitioner” letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MED WATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

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We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

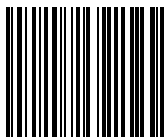
If you have any questions, call Joanne M. Holmes, M.B.A., Clinical Reviewer, at (301) 827-2090.

Sincerely,

Wiley A. Chambers, M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products, HFD-550
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Xalatan
latanoprost
ophthalmic solution

Xalatan
latanoprost
ophthalmic solution



0818057000

Xalatan[®]

latanoprost ophthalmic solution

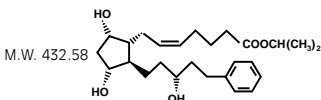


Pharmacia
& Upjohn

0.005% (50 µg/mL)

DESCRIPTION

Latanoprost is a prostaglandin $F_{2\alpha}$ analogue. Its chemical name is isopropyl-(Z)-7-[(1R,2R,3R,5S) 3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate. Its molecular formula is $C_{26}H_{40}O_5$ and its chemical structure is:



Latanoprost is a colorless to slightly yellow oil which is very soluble in acetonitrile and freely soluble in acetone, ethanol, ethyl acetate, isopropanol, methanol and octanol. It is practically insoluble in water.

XALATAN Sterile Ophthalmic Solution is supplied as a sterile, isotonic, buffered aqueous solution of latanoprost with a pH of approximately 6.7 and an osmolality of approximately 267 mOsmol/kg. Each mL of XALATAN contains 50 micrograms of latanoprost. Benzalkonium chloride, 0.02% is added as a preservative. The inactive ingredients are: sodium chloride, sodium dihydrogen phosphate monohydrate, disodium hydrogen phosphate anhydrous and water for injection. One drop contains approximately 1.5 µg of latanoprost.

CLINICAL PHARMACOLOGY

Mechanism of Action

Latanoprost is a prostanoid selective FP receptor agonist which is believed to reduce the intraocular pressure by increasing the outflow of aqueous humor. Studies in animals and man suggest that the main mechanism of action is increased uveoscleral outflow.

Pharmacokinetics/Pharmacodynamics

Absorption: Latanoprost is absorbed through the cornea where the isopropyl ester prodrug is hydrolyzed to the acid form to become biologically active. Studies in man indicate that the peak concentration in the aqueous humor is reached about two hours after topical administration.

Distribution: The distribution volume in humans is 0.16 ± 0.02 L/kg. The acid of latanoprost could be measured in aqueous humor during the first 4 hours, and in plasma only during the first hour after local administration.

Metabolism: Latanoprost, an isopropyl ester prodrug, is hydrolyzed by esterases in the cornea to the biologically active acid. The active acid of latanoprost reaching the systemic circulation is primarily metabolized by the liver to the 1,2-dinor and 1,2,3,4-tetranor metabolites via fatty acid β -oxidation.

Excretion: The elimination of the acid of latanoprost from human plasma was rapid ($t_{1/2} = 17$ min) after both intravenous and topical administration. Systemic clearance is approximately 7 mL/min/kg. Following hepatic β -oxidation, the metabolites are mainly eliminated via the kidneys. Approximately 88% and 98% of the administered dose is recovered in the urine after topical and intravenous dosing, respectively.

Animal studies

In monkeys, latanoprost has been shown to induce increased pigmentation of the iris. The results from the preclinical program demonstrated that the increased pigmentation is unlikely to be associated with proliferation of melanocytes. It appears that the mechanism of increased pigmentation is stimulation of melanin production in melanocytes of the iris stroma.

In ocular toxicity studies, administration of latanoprost at a dose of 6 µg/eye/day (4 times the daily human dose) to cynomolgus monkeys has also been shown to induce increased palpebral fissure. This effect has been reversible and occurred at doses above the standard clinical dose level.

INDICATIONS AND USAGE

XALATAN Sterile Ophthalmic Solution is indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma and ocular hypertension who are intolerant of other intraocular pressure lowering medications or insufficiently responsive (failed to achieve target IOP determined after multiple measurements over time) to another intraocular pressure lowering medication.

CLINICAL STUDIES

Patients with mean baseline intraocular pressure of 24–25 mmHg who were treated for 6 months in multicenter, randomized, controlled trials demonstrated 6–8 mmHg reductions in intraocular pressure. This IOP reduction with XALATAN Sterile Ophthalmic Solution 0.005% dosed once daily was equivalent to the effect of timolol 0.5% dosed twice daily.

CONTRAINDICATIONS

Known hypersensitivity to latanoprost, benzalkonium chloride or any other ingredients in this product.

WARNINGS

XALATAN has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris and periorbital tissue (eyelid) and increased pigmentation and growth of eyelashes. These changes may be permanent.

XALATAN Sterile Ophthalmic Solution may gradually change eye color, increasing the amount of brown pigment in the iris by increasing the number of melanosomes (pigment granules) in melanocytes. The long-term effects on the melanocytes and the consequences of potential injury to the melanocytes and/or deposition of pigment granules to other areas of the eye are currently unknown. The change in iris color occurs slowly and may not be noticeable for several months to years. Patients should be informed of the possibility of iris color change.

Eyelid skin darkening has also been reported in association with the use of XALATAN.

XALATAN may gradually change eyelashes; these changes include increased length, thickness, pigmentation, and number of lashes.

Patients who are expected to receive treatment in only one eye should be informed about the potential for increased brown pigmentation of the iris, periorbital tissue, and eyelashes in the treated eye and thus, heterochromia between the eyes. They should also be advised of the potential for a disparity between the eyes in length, thickness, and/or number of eyelashes. These changes in pigmentation and lash growth may be permanent.

PRECAUTIONS

General: Latanoprost is hydrolyzed in the cornea. The effect of continued administration of XALATAN Sterile Ophthalmic Solution on the corneal endothelium has not been fully evaluated.

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see *Information for Patients*).

Patients may slowly develop increased brown pigmentation of the iris. This change may not be noticeable for several months to years (see **WARNINGS**). Typically the brown pigmentation around the pupil spreads concentrically towards the periphery in affected eyes, but the entire iris or parts of it may also become more brownish. Until more information about increased brown pigmentation is available, patients should be examined regularly and, depending on the clinical situation, treatment may be stopped if increased pigmentation ensues. During clinical trials, the increase in brown iris pigment has not been shown to progress further upon discontinuation of treatment, but the resultant color change may be permanent. Neither nevi nor freckles of the iris have been affected by treatment.

XALATAN should be used with caution in patients with active intraocular inflammation (iritis/uveitis).

Macular edema, including cystoid macular edema, has been reported during treatment with XALATAN. These reports have mainly occurred in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema. XALATAN should be used with caution in these patients.

There is limited experience with XALATAN in the treatment of angle closure, inflammatory or neovascular glaucoma.

XALATAN has not been studied in patients with renal or hepatic impairment and should therefore be used with caution in such patients.

XALATAN should not be administered while wearing contact lenses.

Information for Patients (see **WARNINGS**): Patients should be informed about the possibility of iris color change due to an increase of the brown pigment and resultant cosmetically different eye coloration that may occur when only one eye is treated. Iris pigmentation changes may be more noticeable in patients with green-brown, blue/gray-brown or yellow-brown irides.

Patients should also be informed of the possibility of eyelash changes in the treated eye, which may result in a disparity between eyes in lash length, thickness, pigmentation, and/or number.

Patients should also be informed about the possibility of eyelid skin darkening.

The increased pigmentation to the iris and eyelid, as well as the changes to the eyelashes, may be permanent.

Xalatan

brand of latanoprost ophthalmic solution

Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Patients also should be advised that if they develop an intercurrent ocular condition (e.g., trauma, or infection) or have ocular surgery, they should immediately seek their physician's advice concerning the continued use of the multidose container.

Patients should be advised that if they develop any ocular reactions, particularly conjunctivitis and lid reactions, they should immediately seek their physician's advice.

Patients should also be advised that XALATAN contains benzalkonium chloride which may be absorbed by contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following administration of XALATAN.

If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

Drug Interactions: *In vitro* studies have shown that precipitation occurs when eye drops containing thimerosal are mixed with XALATAN. If such drugs are used they should be administered with an interval of at least five (5) minutes between applications.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Latanoprost was not mutagenic in bacteria, in mouse lymphoma or in mouse micronucleus tests.

Chromosome aberrations were observed *in vitro* with human lymphocytes.

Latanoprost was not carcinogenic in either mice or rats when administered by oral gavage at doses of up to 170 µg/kg/day (approximately 2,800 times the recommended maximum human dose) for up to 20 and 24 months, respectively.

Additional *in vitro* and *in vivo* studies on unscheduled DNA synthesis in rats were negative. Latanoprost has not been found to have any effect on male or female fertility in animal studies.

Pregnancy: Teratogenic Effects: Pregnancy Category C.

Reproduction studies have been performed in rats and rabbits. In rabbits an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XALATAN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XALATAN is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and younger patients.

ADVERSE REACTIONS

Adverse events referred to in other sections of this insert:

Eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; intraocular inflammation (iritis/uveitis); iris pigmentation changes; and macular edema, including cystoid macular edema (see **WARNINGS** and **PRECAUTIONS**).

Controlled Clinical Trials:

The ocular adverse events and ocular signs and symptoms reported in 5 to 15% of the patients on XALATAN Sterile Ophthalmic Solution in the 6-month, multi-center, double-masked, active-controlled trials were blurred vision, burning and stinging, conjunctival hyperemia, foreign body sensation, itching, increased pigmentation of the iris, and punctate epithelial keratopathy.

Local conjunctival hyperemia was observed; however, less than 1% of the patients treated with XALATAN required discontinuation of therapy because of intolerance to conjunctival hyperemia.

In addition to the above listed ocular events/signs and symptoms, the following were reported in 1 to 4% of the patients: dry eye, excessive tearing, eye pain, lid crusting, lid discomfort/pain, lid edema, lid erythema, and photophobia.

The following events were reported in less than 1% of the patients: conjunctivitis, diplopia and discharge from the eye.

During clinical studies, there were extremely rare reports of the following: retinal artery embolus, retinal detachment, and vitreous hemorrhage from diabetic retinopathy.

The most common systemic adverse events seen with XALATAN were upper respiratory tract infection/cold/flu which occurred at a rate of approximately 4%. Chest pain/angina pectoris, muscle/joint/back pain, and rash/allergic skin reaction each occurred at a rate of 1 to 2%.

Clinical Practice: The following events have been identified during postmarketing use of XALATAN in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. The events, which have been chosen for inclusion due to either their seriousness, frequency of reporting, possible causal connection to XALATAN, or a combination of these factors, include: eyelash changes (increased length, thickness, pigmentation, and number of lashes); eyelid skin darkening; intraocular inflammation (iritis/uveitis); corneal edema and erosions; macular edema, including cystoid macular edema; toxic epidermal necrolysis; asthma; exacerbation of asthma; and dyspnea.

OVERDOSAGE

Apart from ocular irritation and conjunctival or episcleral hyperemia, the ocular effects of latanoprost administered at high doses are not known. Intravenous administration of large doses of latanoprost in monkeys has been associated with transient bronchoconstriction; however, in 11 patients with bronchial asthma treated with latanoprost, bronchoconstriction was not induced. Intravenous infusion of up to 3 µg/kg in healthy volunteers produced mean plasma concentrations 200 times higher than during clinical treatment and no adverse reactions were observed. Intravenous dosages of 5.5 to 10 µg/kg caused abdominal pain, dizziness, fatigue, hot flushes, nausea and sweating.

If overdosage with XALATAN Sterile Ophthalmic Solution occurs, treatment should be symptomatic.

DOSAGE AND ADMINISTRATION

The recommended dosage is one drop (1.5 µg) in the affected eye(s) once daily in the evening.

The dosage of XALATAN Sterile Ophthalmic Solution should not exceed once daily since it has been shown that more frequent administration may decrease the intraocular pressure lowering effect.

Reduction of the intraocular pressure starts approximately 3 to 4 hours after administration and the maximum effect is reached after 8 to 12 hours.

XALATAN may be used concomitantly with other topical ophthalmic drug products to lower intraocular pressure. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

HOW SUPPLIED

XALATAN Sterile Ophthalmic Solution is a clear, isotonic, buffered, preserved colorless solution of latanoprost 0.005% (50 µg/mL) supplied in plastic ophthalmic dispenser bottles with a dropper tip and tamper evident overcap.

NDC 0013-8303-04

2.5 mL fill, 0.005% (50 µg/mL), in cartons of 1 & 6.

Storage: Protect from light. Store unopened bottle under refrigeration at 2° to 8°C (36° to 46°F).

Once opened the 2.5 mL container may be stored at room temperature up to 25°C (77°F) for 6 weeks.

R_x only

U.S. Patent Nos. 4,599,353; 5,296,504 and 5,422,368.

Manufactured for:
Pharmacia & Upjohn Company
Kalamazoo, MI 49001, USA

By:
Automatic Liquid Packaging, Inc.
Woodstock, IL 60098, USA

Revised December 1999

818 057 000

Sample
NDC 0013-8303-98
Xalatan®
latanoprost
ophthalmic solution
Sterile
0.005% (125 µg/2.5 mL)

Rx only

Usual dosage: 1 drop in the affected eye(s) in the evening.

Store unopened bottle under refrigeration at 2° to 8°C (36° to 46°F). Protect from light.

Opened bottle may be stored at room temperature up to 25°C (77°F) for 6 weeks.

Keep out of reach of children.



Fill volume
2.5 mL →



Pharmacia & Upjohn

Each mL contains:
latanoprost,
50 micrograms;
benzalkonium chloride,
0.2 mg; sodium chloride,
sodium dihydrogen
phosphate, disodium
hydrogen phosphate.

Manufactured for:

Pharmacia & Upjohn
Company
Kalamazoo, MI
49001, USA

By:

Automatic Liquid
Packaging, Inc.
Woodstock, IL 60098

U.S. Patent Nos.
4,599,353; 5,296,504
and 5,422,368.

818 317 000A

NDC 0013-8303-98

Complimentary Package
Not for Sale

Xalatan®
latanoprost
ophthalmic
solution

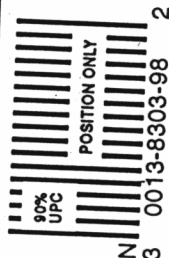
Sterile

0.005%
(125 µg/2.5 mL)

One 2.5 mL
bottle



Pharmacia
& Upjohn



LOT
EXP



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